Chapter 4: The Physics and Biophysiology of Radiation Therapy

George E. Laramore

The use of ionizing radiation in medicine dates back almost to the very date of its discovery. In 1895 Wilhelm Roentgen discovered x-rays, and 3 years later Pierre and Marie Curie announced that they had isolated radium from pitchblende. The first documented radiation biology experiment was performed inadvertently at about this time, when Antoine Becquerel developed a "burn" on his chest from carrying a vial of radium salt in his vest pocket. It soon became apparent that this newly discovered entity - radiation - had the ability to effect profound biologic change. The public embraced this new agent, and it was touted as a cure for almost every ailment known to mankind. The results of these early clinical trials are not well documented, but it is probably safe to assume that most were not very successful. However, the first "cure" of a malignant neoplasm achieved with ionizing radiation was reported in 1899 (Coutard, 1934).

During the early 1900s most clinical radiotherapy was done by surgeons who used it as another form of cautery. Radiation was used in large doses to produce a "tissue slough", and the side effects associated with its early use still color the attitudes many physicians have toward radiotherapy. Used in the proper way, ionizing radiation produces selective modifications of cells via subtle changes introduced into DNA and other cellular elements. Special training is required to understand these effects and how to best use them in clinical settings. From this need, radiation oncology has emerged as a separate medical specialty.

The capabilities of the radiation oncologist have increased in keeping with advancing technology. Initially, only low-energy x-rays were available, and these were capable of treating only superficial tumors, without causing severe side effects to the intervening normal tissues. High-energy linear accelerator were then developed for research purposes and soon were used to produce "megavoltage" x-rays for medical use in a few large centers. However, the "megavoltage" era in radiotherapy really began with the use of gamma ray beams from ^{60}Co sources. Now compact linear accelerators are used routinely in radiotherapy departments. Similarly, research into nuclear physics made it possible to produce many artificial radioisotopes that have had application in medicine; the field is no longer restricted to ^{226}Ra as it was in the past. Investigation in new areas such as particle beam radiotherapy, radiation protecting agents, hypoxic cell sensitizers, and hyperthermia is taking place today and has the potential for changing the field of radiotherapy as much in the future as it has in the past.

The purpose of this chapter is to provide the clinician with an overview of the basic principles of physics and biophysiology that underlie modern radiotherapy. Limitations of space necessitate the presentation of the overall picture only, rather than a detailed chronologic account of the development of the field. Topics will be covered in a manner that assumes no prior expertise on the part of the reader. The references cited will be representative and illustrative in nature rather than comprehensive.

Basic Overview or Physics

Conventional types of radiation

Radiotherapy is performed most commonly using high-energy photons or "quanta" of electromagnetic radiation. The electromagnetic spectrum is a continuum with radiowaves 10 to 1000 meters in length lying at one end and energetic cosmic rays of length 10^{-12} cm lying at the other end. The gamma rays produced from a ^{60}Co source are about 1.3 million electron volts (MeV) in energy, which corresponds to a wavelength of 10^{-10} cm. Energies of 3-5 electron volts (eV) are needed to break chemical bonds, and this typically requires photons of length shorter than 10^{-4} cm. Microwaves used for heating purposes are less energetic than this and act by exciting bending and rotational modes in molecules (eg, H_2O).

High-energy photons used in radiotherapy initially interact in matter (ie, tissue) to produce high-energy electrons by one of three principal processes: photoelectric effect, Compton scattering, or pair production. In the photoelectric effect a photon excites a tightly bound, inner-shell electron and is completely annihilated. This process scales like Z^3/E^3 per gram of material where *Z* is the "effective" nuclear charge of the material and *E* is the photon energy. This process is most important for photon energies in the range of 10 to 50 kiloelectron volts (keV), which is the range typically used in diagnostic radiology. The higher effective "Z" of bone relative to soft tissue causes it to show up well on diagnostic films.

The Compton effect is most important in the 500 kev to 10 MeV range of photon energies used in therapy. It scales like Z^0 per gram of material and decreases in a complex way with increasing energy. Physically, one can think of a photon transferring a part of its energy to a loosely bound outer electron and emerging at a lower energy and longer wavelength. Within this energy range all tissues absorb photons at about the same rate on a gram-for-gram basis. This is important for therapeutic purposes, such as when treating soft-tissue tumors adjacent to bone. On films exposed with megavoltage x-rays the distinction between bone and soft tissue is lost.

Pair production refers to a high-energy photon being annihilated in the strong electromagnetic field of an atomic nucleus and producing an electron-positron pair. The threshold energy for this process is 1.02 MeV. It scales like Z per gram of material and increases with increasing photon energy. For a 10 MeV photon, this accounts for about 28% of the total absorption cross section in tissue. Other processes can also take place at still higher photon energies.

Once one of these primary processes has occurred, a high-energy electron is produced, which creates secondary ionization events as it travels through tissue. Typically, about 34 eV of energy is lost for each ion pair that is produced. The resulting ionization clusters are relatively isolated on a scale of typical cellular distances. Most of the events involve water molecules in the cell cytoplasm, and their reaction products initiate complex sequences of chemical reactions that generally involve free radicals. The biologic properties of different megavoltage photon beams are equivalent per unit of energy deposited.

Radiation doses are thus specified in terms of the energy deposited in a unit quantity of material. In the past the conventional dose unit was the rad, which was equivalent to 100 ergs being deposited per gram of material. More recently an international commission (Wyckoff et al, 1975) has agreed that radiation doses should be specified in terms of gray (Gy), which corresponds to 1 joule being deposited per kilogram of material. The older literature will have radiation doses specified in terms of rad, whereas the newer literature will have the doses specified in terms of gray. Doses in this chapter will be specified in terms of the latter unit. Numerically, one can convert doses in rad to equivalent doses in Gy by dividing by 100 (ie, 100 rad = 1 Gy).

Typical depth-dose curves for photon beams used in the therapy of head and neck cancers are shown in the upper panel of Fig. 4-1. The plots are for the dose along the central axis for a 10-cm x 10-cm field size. The energy of the beam is specified by the energy to which the incident electron beam is accelerated before impacting the target and actually producing the x-rays. The x-ray beam itself is a continuum with the maximum energy equal to that of the electron beam. To express the fact that a range of x-ray energies is produced, the term *MV* is used rather than *MeV*. Appropriate filtering elements are also used to "harden" and "shape" the beam. but for most practical purposes at a given source-axis distance (SAD), the beams from given energy linear accelerators are essentially equivalent. The three curves have the same general shape but vary somewhat in specific details. Note that they do not start out at their maximum value, but rather that initially there is a build-up region. This comes about because the initial, high-energy electrons produced by the photon beam are directed primarily in the forward direction. The number of these electrons increases with depth until a distance equal to the average electronic path length is reached. The deposited dose is thus low at the surface and then rises to a maximum, after which it decreases with depth due to attenuation of the radiation field. The distance of the dose maximum from the surface is referred to as "Dmax". It varies from 1.2 cm for the 4-MV (80-cm SAD) beam, to 1.3 cm for the 6-MV (100-cm SAD) beam, and to 3 cm for the 15-MV (100-cm SAD) beam. The skin and subcutaneous tissues are spared within this build-up region, enabling one to deliver a higher dose of radiation to a deeper tumor. One can use still higher energy photon beams with even greater values of Dmax, but these have increased usefulness for the more deeply seated tumors of the thorax, abdomen, or pelvis.

Alternatively, one can directly use the high-energy electron beam produced by the linear accelerator in patient treatments. Typical depth-dose curves for various electron energies are shown in the lower panel of Fig. 4-1. Note that these beams typically penetrate a given distance and then fall off quite rapidly. There is a slight amount of skin sparing for the 6 MV beam but not for the others. These beams are useful for treating skin cancers, tumors of the buccal mucosa, or even superficial tumors of the oral cavity, provided that appropriate applicator cones are used (eg, see Wang et al, 1983). Optimal treatment of a given lesion may require some combination of electron and photon beams (Tapley, 1980), and this in turn requires the services of a comprehensive radiation treatment facility. Megavoltage electron beams have the same biologic properties of megavoltage photon beams for an equivalent dose of absorbed radiation.

Particle radiation

In the strictest sense the electron beams used in conventional radiotherapy facilities are a type of "particle" radiation, but this section will be devoted to he heavier charged particles (eg, protons, alpha-particles, heavy ions, pi-mesons, and fast neutrons) used experimentally at a small number of radiotherapy centers throughout the world. These particles are of special interest because of their different radio-biologic properties and/or their better depth-dose characteristics, which allow for higher tumor doses without causing a commensurate increase in the dose to the surrounding normal tissues.

The particle for which there has been the greatest amount of clinical work to date is the fast neutron. A depth-dose curve for a beam from one of the new NCI-sponsored cyclotron facilities is shown in the upper panel of Fig. 4-2. Note that this is similar in general appearance to the photon beam curves in Fig. 4-1. Fast neutrons are of clinical interest because of their radiobiological properties, which arise because of the much greater amount of energy they deposit when they go through tissue. Neutrons are neutral particles and interact with the atomic nuclei, producing "heavy" charged particles such as protons, alpha-particles, or nuclear fragments that in turn create a dense chain of ionization events as they go through tissue. The distribution of these secondary particles depends on the energy spectrum of the neutron beam, and hence the biologic properties of the beam are strongly dependent on its energy spectrum. Neutrons used in therapy are generally produced by accelerating charged particles such as protons or deuterons and impacting them on a beryllium target. To a first approximation one can specify the beam by indicating the charged particle that is accelerated, the energy of the particle when it impacts the target, and the distance between the target and the treatment axis (SAD). The curve in Fig. 4-2, for example, is for a 10-cm x 10-cm field for a beam produced by accelerating a stream of protons to 50 MeV and impacting them on a beryllium target. It has approximately the same penetration characteristics as the photon beam from a 6-MV linear accelerator. Most often cyclotrons are used to accelerate the charged particle beams, but special linear accelerators can be used as well.

Neutrons are also produced using deuterium-tritium (DT) generating tubes that yield a quasi-monoenergetic beam of 14 to 15 MeV neutrons. Although the cost of systems using the DT reaction is lower than cyclotron-based systems, their lower neutron output makes them less suitable for therapy. Such DT systems are now used for clinical purposes only in a few centers in Europe. Neutrons in the energy range most commonly used in therapy deposit most of their energy via a "knock-on" reaction whereby a hydrogen nucleus is impacted, producing a recoil proton. This process is more efficient in tissues that contain a greater quantity of hydrogen, such as adipose or nerve tissue, and less efficient in bone. Compared with muscle, the absorption can vary by ± 10% (eg, see Catterall and Bewley, 1979). Typically, the recoil fragments produced by therapy neutron beams deposit 50 to 100 times more energy than the electrons created by megavoltage photon beams. The energy deposited by a radiation beam is characterized by its linear energy transfer (LET) spectrum. The primary high-energy electrons produced by megavoltage photons have LETs in the range of 0.2 to 2 keV per micron traversed whereas the recoil protons produced by fast neutrons have LETs in the range of 20 to 100 keV per micron. It is this difference in LETs that gives rise to the special radiobiologic properties discussed in the next section.

There is also considerable interest in using the charged particle beams directly for therapeutic purposes. This generally requires beams of much higher energy than used to produce neutrons. The lighter particles such as protons and alpha-particles are of interest because of their extremely favorable depth-dose characteristics. The radiobiologic properties of these beams are similar to those of conventional photon or electron beams. Heavy charged particles, on the other hand, combine the favorable depth-dose properties of the proton and alpha-particle beams with the favorable biologic properties of the neutron beams. Energies are on the order of several hundred MeV per nucleon rather than the few MeV per nucleon for the recoil fragments produced by neutrons. These highly energetic particles do not deposit much energy in tissue until they reach the end of their path, where they are moving quite slowly. Hence, they do not produce much radiation damage in the intervening tissues.

The lower panel shows both a "pure" Bragg peak for a neon beam (solid line) as well as its spread form (dotted line). These data are from the BEVALAC facility at the Donner Laboratories in Berkeley, California. Note the high ratio of the energy deposited at the peak compared with that deposited at shallower depths for the unspread beam. The Bragg peak itself is quite narrow, and so it must either be "scanned" across a tumor while its penetration depth is being varied, or it must be spread out by passing it through appropriate filters. True three-dimensional scanning is still in the experimental stage and not available for treating patients. The dotted curve shows the result after the beam is passed through a 4-cm spiral ridge filter (SRF). Note that this both lowers the peak-to-plateau ratio of energy deposition and at the same time broadens the trailing edge of the peak. Clearly, both these things are undesirable for therapeutic purposes. However, the dose of radiation deposited along the initial portion of the path is still lower than that deposited across the spread peak, which represents an advantage over the other types of radiation discussed thus far in this chapter. The broadening of the trailing edge of the peak occurs because of fragmentation of the neon nuclei in the filter, and this does not occur with protons or alpha-particles. Thus, the spread peaks for the latter two particles have somewhat better localization than the curve shown here.

Another type of charged particle that is being used in radiotherapy is the pi-meson. The pi-meson is a subatomic particle produced by accelerating protons to energies in the range of 400 to 800 MeV and then impacting them into an appropriate target. Magnetic fields are then used to focus the resulting pi-mesons into a beam that can be used for therapy. The pi-meson is much lighter than the other charged particles discussed in this section, being only 273 times the mass of the electron (the proton, for example, is 1836 times the mass of the electron). Like the other charged particles, it does not lose much energy until it is near the end of its path, resulting in a "Bragg-peak" type of energy deposition curve. However, when it stops, an atomic nucleus "captures" it and then explodes into massive charged fragments that, in turn, deposit considerable energy in a very localized region. Neutrons are also produced in this process, and they deposit their energy throughout a somewhat greater volume. The biologic properties of a pi-meson beam are hence very complex because of the larger number of processes involved, but in a crude sense, it can be thought of as behaving like a mixture of low-LET and high-LET radiation.

Fundamentals of Radiobiology

Cell killing by radiation

Within the cell there are certain key "targets" that must be affected by the radiation before the cell is killed. The nuclear DNA is probably the most critical target, but other elements such as the nuclear membrane may be important as well. When any form of radiation interacts with the cell material, there is some probability that one or more of the key target areas will be directly involved. This is the "direct" mechanism of action. Conversely, the radiation interaction may be with some other element such as a molecule in the cell's cytoplasm, and the loss of this molecule may not be critical to the cell's continued function. The reaction products may, however, be capable of damaging the critical targets provided that they can diffuse to them and interact before being converted to nontoxic elements by other chemical interactions (for the OH radical produced by the interaction of radiation with H_2O in the cell, the diffusion distance is about 2 nm). This is the "indirect" mechanism of action. All forms of radiation interact by both mechanisms, but because of the smaller amount of energy deposited by low-LET radiation, it primarily interacts via the "indirect" mechanism. High-LET radiation, on the other hand, kills a significant fraction of cells via the "direct" mechanism. Comparing the biologic effects of low- and high-LET radiation provides a way of studying the results of these two processes.

Perhaps the simplest biologic experiment imaginable is simply to irradiate a colony of cells with different amounts of a given type of radiation and see how many are still alive and able to reproduce afterward. This is done by plating the cells out on a new growth medium and counting the resulting colonies. This assays for a reproductive viability that is the quantity of paramount importance in tumor control. The radiation is given in a single dose, and the cells are plated out immediately.

A plot of the surviving fraction of cells as a function of the radiation dose is shown. By convention, the surviving cell fraction is plotted on a logarithmic scale, and the radiation dose is plotted on a linear scale. This curve is representative of most mammalian cells. Consider first the solid curve, which represents the survival data. Note that there are two distinct regions to the curve. There is an initial region for low radiation doses where the slope of the curve is shallow. In this region small incremental changes in the amount of radiation are not very effective at increasing the number of cells that are killed. This is called the *shoulder* region, and its width is characterized by the parameter D_q. It is the distance along the dose axis at a surviving fraction of unity between the abscissa and the point where the extrapolate linear portion of the curve is intersected. It is a measure of the ability of the cells to repair small amounts of radiation damage.

At higher doses of radiation the curve becomes a straight line on a semilog plot. Its slope is characterized by D_o, which is the incremental dose change required to reduce the surviving cell fraction to 1/e of its value. The steeper the slope in this region, the smaller is the value of D_0 and the more radiosensitive is the cell line. When extrapolated back to a zero radiation dose, it intersects the abscissa at a value N. One can model a curve of this type using the equation:

$$\mathbf{S = 1 - (1 - \exp(- D/D_0))^N}$$

where S is the surviving fraction, D is the radiation dose, and N and D_0 are as indicated in the figure. In target theory N can be though of as the number of distinct targets in the cell that must receive one radiation "hit" before the cell is inactivated. One can also introduce other parameters into the analysis by requiring more than one radiation "hit" to inactivate a given target, but such refinements are beyond the scope of this overview. Radiobiologic data can also be analyzed using a linear-quadratic model of the form:

$$S = \exp(-\alpha D - \beta D^2)$$

where alpha and beta are simply parameters used to fit the curve over some restricted dose range (Kellerer and Rossi, 1971). Large beta/alpha ratios correspond to curves with large shoulder regions. There is one final point to note. If one gives 5 Gy resulting in a 10% cell survival and then waits 6 to 9 hours before giving additional radiation, the shoulder region of the survival curve is regenerated as shown by the dashed curve. During the waiting period, the cells have recovered most of their original ability to recover from small doses of radiation. This is called *sublethal damage repair.*

The basic features of the cell survival curves can be qualitatively understood in terms of DNA repair processes as outlined. The complementary strands of the helix are represented by the parallel straight lines, and the base pairings between the strands are represented by the open circles and dots that link the lines. In the upper panel a photon schematically interacts with one strand of the DNA. This could either be via the direct or the indirect mechanism, with the particular nature of the damage event being irrelevant to the present discussion. What is important is that only one strand of the DNA is affected. Most cells contain repair enzymes that can excise the damaged portion and then, using the information on the complementary strand, can resynthesize the damaged portion. This is what is taking place in the shoulder region of the cell survival curve. If small amounts of radiation are given, then there is a high likelihood that many cells will experience only one damage event that can be repaired in this manner. However, when larger amounts of radiation are given, then we have the situation shown in the lower panel. Now many of the cells experience multiple damage events, and there is increased probability that some cells will have damage to both strands of the DNA. When the cell attempts to repair the radiation damage, a portion of both strands is excised and a portion of the genetic information is lost. If this information loss occurs in a "silent" region of the DNA, then the cell continues to live. On the other hand, if the information loss occurs in a key area of the genome, then the cell ultimately dies. This is the situation that occurs in the straight portion of the cell survival curve.

Relative biologic effectiveness (RBE) and oxygen enhancement radio (OER)

High-LET radiation deposits so much energy as it goes through the cell that radiation damage events are clustered closely in space and time. This means that if one strand of the DNA is damaged, there is a high probability that the other strand will be damaged as well. Thus, we have the situation shown in the lower panel, with an increasing portion of the radiation damage being irreparable. Hence, as the LET of the radiation is increased, we expect to see the shoulder of the cell survival curve decrease in size (ie, $D_q \rightarrow O$), and the slope of the straight portion of the curve become steeper (ie, $D_o \rightarrow O$). This effect is shown with survival curves of human kidney cells exposed to 250 kVp x-rays, 15 meV neutrons from a D-T generator, and 4 MeV alpha-particles. The LET of the radiation increases as indicated,

and the curves change as expected.

Because the shapes of the cell survival curves shown differ according to the type of radiation used, it is difficult to define biologically equivalent doses for therapeutic purposes. Consider the neutron and the curves, for example. If we choose as an endpoint the amount of radiation required to kill 99% of the cells, this requires about 9.3 Gy of x-rays but only about 4.2 Gy of neutrons. Hence on a physical dose basis, the neutrons are more effective, and we can define a relative biologic effectiveness (RBE) of 9.3/4.2 = 2.2. On the other hand, if we choose as an endpoint the amount of radiation required to kill 50% of the cells, then the respective doses are 2.8 Gy of x-rays and 1.1 Gy of neutrons for an RBE of 2.5. This situation illustrates a general phenomenon: because of the increased shoulder on the cell survival curves for low-LET radiation, the RBE for neutrons and other high-LET radiation increases with lower dose increments. The change is greatest for cell lines that have the largest shoulders on the low-LET curves (eg, gut, nerve tissue) and is smallest for cell lines having small shoulders (eg, bone marrow, germ cells) (Hall, 1988). In the early days of neutron radiotherapy, workers did not appreciate the dependence of the RBE on dose size and tissue type, which led to a high incidence of treatment-related complications. These effects are now being taken into account, and the incidence of complications is much lower.

Earlier in this chapter it was noted that low-LET radiation primarily killed cells via the "indirect" mechanism, which involved the radiation interacting with molecules in the cell cytoplasm. The sequence of chemical reactions that can take place is quite complex, but at some point a free radical is generally involved. A free radical is a chemical species that contains an unpaired electron and is highly reactive. Oxygen acts to stabilize the free radicals, thus allowing them to diffuse to the DNA or other target regions where they react chemically to produce damage. An obvious question is how great an oxygen concentration is required. Experiments have been performed on many species of bacteria, yeasts, and mammalian cells; the overall conclusions are summarized and show the relative radiosensitivity as a function of the oxygen concentration in Torr (1 Torr = 1 mm of mercury). Note that the radiosensitivity does not change much until the oxygen concentration drops below about 20 Torr, and then falls off fairly rapidly. At essentially 0 Torr the cells are 2.5 to 3.0 times less radiosensitive than they are on the flat portion of the curve. Normal tissues of the body are at oxygen concentrations between that of arterial and venous blood - between 40 to 100 Torr - and so are on the radiosensitive portion of the curve. However, large tumors tend to outgrow their blood supply and develop regions of necrosis surrounded by cells in a very hypoxic state. These tumor cells thus lie on the radioresistant portion of the curve, and this is thought to be one reason why large tumors are not as well controlled by radiotherapy as small ones.

A way of avoiding this problem is to use a mode of radiotherapy that is not as dependent on the presence of oxygen for cell killing. One possibility is to use high-LET radiation for which the "direct" mechanism of cell killing is more important. Cell survival curves for human kidney cells irradiated in both well-oxygenated and hypoxic conditions are shown. If we choose as our endpoint a 90% cell kill, then for 250 kVp x-rays it takes 2.5 times as much radiation to kill hypoxic cells as it does when they are well oxygenated. The oxygen enhancement ratio (OER) is thus 2.5. As the LET of the radiation increases - going to 15 MeV neutrons from a D-T reaction and then to 4 MeV alpha-particles, and finally to 2.5 MeV alpha-particles - the OER decreases to 1. This shows the effect of the increasing importance of the "direct" mechanism as the LET of the radiation increases. In general, the

OER decreases with increasing LET until a value of 1 is reached for a LET of about 150 meV/micron.

Cell cycle effects

Cycling mammalian cells proliferate by undergoing mitotic divisions. To define terms, let us take mitosis or M phase as our starting point. After this comes a "resting" phase, G_1, before the cell starts undergoing DNA synthesis. Following DNA synthesis (S), there is another "resting" phase, G_2, before the cell again enters mitosis. Although it is well recognized that many chemotherapeutic agents act at specific points along the cell cycle, it is not commonly appreciated that cells vary in their degree of radiosensitivity according to their position in the cell cycle. Synchronously dividing cell populations are needed in experiments that measure this effect. One way of producing such a cell population is to exploit the fact that at the time of mitosis, many cells growing in monolayers attached to the surface of culture containers will take on a spherical shape and become very loosely attached to the vessel wall. If the container is subjected to a gentle shaking motion, these cells will become detached and float to the surface of the growth medium where they can be collected. These cells can then be inoculated into a fresh growth medium, where they will grow in synchrony through several cell cycles. One can then perform radiobiologic experiments on these cells at different times after "shake-off" and catch them at different points along the cycle.

The result of radiosensitivity measurements for typical mammalian cells is shown. Relative radio resistance is shown along the abscissa as a function of position along the cell cycle. The position of the cells along the cycle is shown at the top. The cells are quite radiosensitive early in the M phase but become more resistant toward the end of this phase. They are resistant in the early G_1 phase but then become more sensitive in the late G_1 and early S phases. They then become sensitive again in the late G_2 and M phases. Cell lines vary in the time they require to go through the cycle, but this is mostly caused by different lengths of the G_1 phase. The exact mechanisms underlying this change in radiosensitivity are not clear, but it is interesting to note that at the beginning of mitosis the DNA in the chromosomes aggregates into a discrete state, whereas in the late S phase the DNA content of the cell has doubled. These points in the cycle correspond, respectively, to the points of maximum and minimum radiosensitivity. Other variations in radiosensitivity compounds in the cell. Sulfhydryl compounds act as free radical scavengers and so act to protect the cell from the "indirect" effects of radiation.

Specific cell survival curves for Chinese hamster ovary cells at different points along the cell cycle are shown (Gragg et al, 1977, 1978; Meyn, 1984). The open symbols are for cells exposed to gamma rays from a ^{60}Co source, and the closed symbols are for cells exposed to a fast neutron beam. The point to note is that for each form of radiation there is the same type of variation along the cell cycle, but the degree of variation is about a factor of 4 less for the neutron beam. OERs are about the same for different points along the cycle, so this represents an effect apart from this.

Many tumor systems contain an appreciable fraction of cells in a noncycling or G_0 phase. Radiation damage to cells in this phase cannot be monitored until the cells are recruited back into the cycle and one can see whether or not they produce viable progeny.

Noncycling cells can be produced in the laboratory by allowing then to grow in a medium until some key nutrient is exhausted. Cell proliferation then stops, and if the cells are kept in this suboptimal medium, the number of cells remains constant. Such cells are said to be in the "plateau" phase of growth (Hahn and Little, 1972) and are mostly in the G_0 phase. These cells can be irradiated and then can either be immediately inoculated into fresh growth medium or can be incubated for a period of time in the suboptimal medium before the inoculation takes place. Once they are placed in the fresh growth medium, they return to their normal cycling mode. However, the cell survival curve varies depending on whether or not they have been incubated for a time before being placed in the fresh medium.

This effect is shown. The circular data points indicate cells treated with ^{60}Co radiation, and for a given dose of radiation there are more surviving cells after an 8-hour delay than if the cells immediately started cycling. This effect is called *potentially lethal damage repair* because the effect of the radiation damage depends on what happens to the cell after the irradiation. The dose is only "potentially" but not necessarily lethal to the cell because the cell can repair itself before reentering the mitotic cycle where it is expressed. The square data points are for cells irradiated with 50 MeV D->Be neutrons. For high-LET radiation, potentially lethal damage cannot be repaired (or can be repaired only to a very limited extent), a fact that may be important in certain clinical settings.

Therapeutic Window Concept

Dose response curves for both tumor control and normal tissue damage are sigmoidal in shape. Whether or not radiation can safely control a given tumor depends on the relative positions of these two curves. Dose response curves for a "radiosensitive" tumor are shown. Here, giving a therapeutic dose of radiation results in a 95% probability of tumor control and only a 5% probability of normal tissue complication. There is a large gap between the two curves - that is, there is a wide "therapeutic window". This should be contrasted with the situation shown for a "radio resistant" tumor. In this situation a dose of radiation that would result in a 95% probability of tumor control would result in an unacceptably high probability of normal tissue damage. Giving doses that are within the limits of normal tissue tolerance would yield only a low likelihood of tumor control, and the separation between the two curves is very narrow. Clearly, the concept of a "therapeutic window" depends on the radiobiologic properties of both the tumor and the normal tissue in the irradiated volume.

In general, one can improve local control of tumors by improved dose localization, which means moving higher on the tumor response curve without moving higher on the normal tissue complication curve, or by exploiting some intrinsic difference in the properties of the tumor and normal tissues, which effectively widens the gap between the two curves. Three-dimensional treatment planning and delivery, brachytherapy, intraoperative radiotherapy, and the use of charged particle radiation are examples of the former approach; the use of high-LET radiation, altered fractionation schedules, radiosensitization agents, and radioprotective agents are examples of the latter.

Clinical Correlation

Fractionated radiotherapy

The intent of clinical radiotherapy is to sterilize tumors while at the same time avoiding untoward damage to the normal tissues in the treatment volume. To accomplish this goal, fractionated schemes of delivering radiotherapy have evolved over time. Both the tumor and the normal tissue consist of heterogeneous populations in regard to the position of the cells in the cycle. In addition, the tumor may have an appreciable fraction of its cells in a hypoxic state. It is shown what happens when such a mixture of cells is irradiated with equal-dose fractions of magnitude D. The first dose increment preferentially kills the cells that are well oxygenated and are in radiosensitive portions of the cell cycle. Suppose one then waits several hours before delivering the next dose increment. During this period there is, of course, repair of sublethal damage. With the killing of a substantial number of cells, there is less competition for the available oxygen, hence some of the formerly hypoxic cells can reoxygenate. Also, some of the cells can proceed along the cell cycle and thus be in a more radiosensitive phase when the next dose of radiation is delivered. Assuming that both effects occur, the result is the solid curve shown. If there is no reoxygenation and/or redistribution throughout the cell cycle, then the result is the dotted curve, which shows less cell kill because the remaining cells are in a radioresistant state. These are not the only effects: there is continued cell division and regrowth during the time interval between radiation fractions. These tumor repopulation kinetics have not been taken into account. To maximize the cell kill, it is important that the size of the dose fractions be greater than D_q - the width of the shoulder region of the single fraction cell survival curve.

These effects are known as the four Rs of radiotherapy: (1) repair (of sublethal damage), (2) redistribution (across the cell cycle), (3) repopulation, and (4) reoxygenation. Fractioned radiotherapy has evolved to exploit the differences in these effects between tumors and normal tissues. With few exceptions radiotherapy works not because tumors are intrinsically more radiosensitive than normal tissue (ie, a smaller value of D_0), but because normal tissues are better at repair and repopulation.

Time-dose considerations are important in estimating the effect of a given total radiation dose. If the dose were given all at once, then the normal tissues would experience more cell killing than if it were given in a fractionated manner. This difference occurs because single fractions allow no opportunity for sublethal damage repair. In general, smaller total radiation doses given over shorter total treatment times produce the same normal tissue effects as larger total radiation doses given over longer time intervals. The classic measurements that illustrate this point are the isoeffect measurements on skin that were made by Strandquist (Strandquist, 1944). He showed that the isoeffect lines for various degrees of skin damage and for curing skin cancer were straight when plotted on a log-scale of total dose versus time. Moreover, the lines appeared to have the same slope (ie, were parallel). The required dose to produce a given effect was proportional to time to the 0.33 power. Additional work has been done on pig skin by Fowler and Stern (Fowler and Stern, 1960). They found that a moist skin desquamation could be produced by giving either 20 Gy in 1 fraction, 30 Gy in 5 equal fractions over 5 days, or 50 Gy in 20 equal fractions over a 28-day period (treating 5 days per week as in conventional radiotherapy schedules). Ellis (1967) extended this concept to clinical radiotherapy by allocating a portion of the exponent 0.33 to the overall

treatment time, T, and a portion to the number of fractions, N. He defined the nominal standard dose (NSD) by:

$$\mathbf{NSD = D_t/(T^{0.11}\ N^{0.24})}$$

where D_t is the total radiation dose. The exponents in this expression are for skin and no doubt vary for other tissues. However, the above expression provides a crude way of comparing different dose fractionation schemes.

Altered fractionation schedules

The highly fractionated radiotherapy schemes used today are the result of many years of clinical experience, but radiobiologic considerations may provide guidance for their future improvement. For example, acute radiation side effects such as mucositis and pharyngeal edema are caused by changes in tissues that are composed of rapidly proliferating cells. Late effects such as subcutaneous fibrosis, vascular damage, radiation necrosis, and spinal cord injury are caused by changes in tissues composed of more slowly proliferating cells. Radiobiologic measurements indicate that for low-LET radiation, the tissues experiencing late effects are characterized by cell survival curves having large shoulders (Withers et al, 1982). It is the late effects that ultimately limit the total dose that can be delivered in the treatment of head and neck cancer. Hence, a logical approach would be to give smaller radiation treatment fractions so as not to exceed the shoulder on the "late effects" tissue curves and then to go on to give a higher total dose, which, it is hoped, would result in greater tumor control. This would effectively widen the therapeutic window. Note that the assumption is implicitly made that the tumor will behave like the rapidly proliferating normal tissues and thus will not have a large shoulder on its cell survival curve. To avoid too great a prolongation of the overall treatment time and hence allowing tumor repopulation kinetics to dominate, multiple daily fractions must be given. A sufficient time interval (generally ≥ 6 hours) must elapse between the multiple daily treatments to allow for adequate repair of sublethal and potentially lethal damage in the normal tissues.

Hyperfractionation refers to giving multiple daily doses of radiation of such a size that the overall treatment time is about the same as for conventionally fractionated course of once-a-day radiotherapy. The Radiation Therapy Oncology Group (RTOG) has been systematically exploring this approach using twice-daily treatments of 1.2 Gy each. The first RTOG trial randomized 210 patients with locally advanced head and neck cancers to 60 Gy given in this manner versus conventional radiotherapy (Marcial et al, 1987). There was no difference in either local or regional control or survival between the two arms, but the acute effects of the hyperfractionation schema were well tolerated. Next, the RTOG launched a hyperfractionation dose-searching study to determine the maximum safe dose that could safely be given for tumors in the head and neck region. Patients were randomized to receive either 67.2, 72, 76.8, or 81.6 Gy total dose using a complex randomization schema (Cox et al, 1990). A preliminary analysis based on 479 patients shows a suggestion of improved local control at 2 years that correlates with increasing radiation dose for the lowest three arms: 25% for 67.2 Gy, 37% for 72 Gy, and 42% for 76.8 Gy ($p = 0.08$). No survival differences were noted. No data has thus far been presented for patients entered on the 81.6 Gy arm. The incidence of soft tissue necrosis was 10% for 67.2 Gy, 5.1% for 72 Gy, and 13.9% for 76.8 Gy.

The European Organization for Research on Treatment of Cancer (EORTC) has also been exploring hyperfractionated radiotherapy. It conducted a phase III trial comparing twice-daily treatments of 1.15 Gy each to 80.5 Gy total dose versus once-daily treatments of 2 Gy each to 70 Gy total dose. Two hundred fifty-four evaluable patients were entered and at 3 years the local/regional control rate was 59% on the hyperfractionation arm versus 43% on the standard arm (Hariot et al, 1988).

Accelerated fractionation refers to giving multiple daily doses of such a size that the overall treatment time is shortened relative to that of conventional radiotherapy. This may have a potential advantage for overcoming repopulation effects in rapidly proliferating tumors (Thames et al, 1983). Wang has employed such a schema in the treatment of advanced head and neck tumors (Wang et al, 1986, 1988). He uses 1.6 Gy fractions twice daily, which is too high a total daily dose for the patient to tolerate without a planned treatment interruption to allow for repopulation and recovery of the mucosa. No randomized trials have been conducted using this schema, but a comparison with historical controls indicates a possible benefit.

The EORTC has conducted a randomized accelerated fractionation trial using 3 daily fractions of 1.6 Gy for 10 days, a 3-week planned treatment interruption to allow for mucosa recovery, followed by a boost to 67.2 Gy total dose (with or without misonidazole - a hypoxic cell sensitizer). These two experimental arms were compared against a standard arm using once-a-day radiotherapy. A total of 523 patients were entered into the study and an initial report indicates no significant differences with respect to either local or regional control or survival among the three arms (van der Bogaert et al, 1986).

Many "hybrid" fractionation schemes have been proposed and reported in the context of phase I studies involving small patient numbers. Although conceptually attractive, nonstandard radiation therapy schemes have inherent toxicities and thus far their clinical benefit is uncertain. Their use at present should be confined to a clinical trial setting.

Brachytherapy

Many radioactive isotopes are used in modern radiotherapy practice. Although radium needles are still used as implants in certain head and neck tumors, the trend is now toward afterloading techniques using ^{192}Ir sources. These sources produce a lower-energy gamma ray, thus simplifying the radiation protection requirements associated with routine patient care. These sources are left in place for a specified time and then are removed. Alternatively, permanent implants using ^{198}Au and ^{125}I can be used. These implants deliver their total radiation dose over the effective lifetime of the radioactive material.

One obvious advantage to using implants for a portion of the planned radiotherapy is better dose localization. This results in less radiation damage to the normal tissue surrounding the tumor. Another advantage is the relatively prolonged time over which the radiation is delivered. External beam radiation is given at the rate of 1.5 to 2.0 Gy per minute. A typical ^{192}Ir implant delivers its dose at the rate of 0.4 to 0.8 Gy per hour. This can be thought of as "continuous" fractionation, and it allows for normal tissue repair and reoxygenation of the tumor throughout the time course of the implant. A typical ^{125}I implant delivers its dose at an even slower rate. Often high total doses in the range of 100 to 200 Gy are given, but one half of the total dose is given over the first 60-day half life, one fourth of the total dose is given

over the next 60-day half life, etc. The actual radiobiology of such extremely low dose rates is somewhat uncertain.

Intraoperative radiotherapy

Over the past two decades there has been increasing interest in both Japan and the USA in radiation therapy directly administered to he exposed tumor bed at the time of surgery. Intraoperative radiotherapy (IORT) is given as a single, large fraction using either orthovoltage x-rays or megavoltage electrons. In this approach it is often possible to move critical structures outside the radiation fields, and the surgeon can aid in identifying the areas at highest risk for residual tumor. A few institutions have dedicated equipment in operating rooms, but the majority of facilities offering intraoperative radiotherapy transport the patient from the operating room to a sterilized unit in the radiation oncology center where the radiation is actually delivered.

Because the biologic effectiveness of a single large dose of radiation is much greater than if the same amount of radiation were given in multiple increments, the total dose given intraoperatively must be reduced compared to that given in a course of fractionated radiotherapy. Most of the IORT experience is for tumors of the abdomen and pelvis, but some general guidelines can be given regarding the tolerance of certain classes of normal structures of importance in the head and neck region. Major blood vessels tolerate single doses in the range of 20 to 25 Gy, whereas damage to peripheral nerves has been noted at doses higher than 20 Gy (Kinsella et al, 1985). On the other hand, tumor hypoxia may be a greater problem when the radiation dose is given in a single increment, because there is no time for reoxygenation to take place. High electron affinic radiation sensitizers such as misonidazole or SR-2508 may have a role to play in future IORT study protocols. Similarly, tumor redistribution kinetics do not have time to operate during IORT, and thus tumor cells in radioresistant parts of the cell cycle may be preferentially spared with this technique.

IORT probably can best be used in situations where there is a limited number of well-defined sites at high risk for microscopic residual disease. Possible indications are (1) tumor fixation to the carotid artery or deep structures of the neck, (2) "close" margins because of the necessity to preserve vital structures, or (3) tumor extending to bony structures such as the base of the skull, spinal column, sternum, or clavicle.

High-linear energy transfer radiation

The greatest body of clinical data on the use of high-LET radiation in the treatment of head and neck tumors is for fast neutrons. This will be the topic of the present section.

Squamous cell carcinomas

The usefulness of fast neutron radiotherapy in the treatment of squamous cell carcinomas of the head and neck is a subject of considerable controversy. The first reported work dates back to the 1940s when Stone and co-workers conducted a series of clinical studies using an early cyclotron at Berkeley (Stone, 1948). A total of 249 patients were treated and about half of these had head and neck tumors. Although many dramatic tumor responses were reported, the late complication rate was unacceptably high. Interest in fast

neutron radiotherapy waned until the late 1950s when a better understanding of fast neutron radiobiology indicated that most of Stone's patients had inadvertently received extremely high doses of radiation. Investigation of fast neutron radiotherapy then began at Hammersmith Hospital and an early report noted dramatic tumor response again, but this time with a more acceptable complication rate (Catterall et al, 1977). Unfortunately, other trials in Europe and the USA failed to confirm this benefit (Duncan et al, 1984, 1987; Griffin et al, 1984, 19890. They showed no improvement in either local control at the primary site or in survival with neutron radiation. However, they seem to demonstrate improved local control for clinically positive neck nodes - 45% versus 26%, $p = 0.004$ (Griffin et al, 1983, 1989). This fact can be qualitatively understood in terms of the basic radiation biology of these tumors. Battermann et al measured the response rates of pulmonary metastases from various tumor histologies using both fast neutrons and conventional photon irradiation (Battermann et al, 1981). They found that the RBE for squamous cell tumors was about the same as for the normal tissue side effects (RBE - 3-3.8), hence one would not necessarily expect a therapeutic gain if some other factor such as tumor hypoxia were not a problem and OER effects would come into play. Guichard et al have demonstrated in animal models that metastatic lymph nodes often have a greater fraction of hypoxic cells than primary tumors of equal size (Guichard et al, 1979). Measurements of oxygen partial pressure in human subjects show that hypoxic regions within cervical lymph node metastases constitute approximately 20% of their volume (Gatenby et al, 1988). Hence, it may be that tumor hypoxia in enlarged cervical lymph nodes and not at the primary tumor site accounts for the clinical observations reported thus far. The RTOG is currently undertaking yet another randomized trial for squamous cell tumors of the head and neck using the more sophisticated treatment techniques now possible with modern neutron radiotherapy. The results of this trial will be of great interest to the radiotherapy community.

Tumors that recur after initial radiotherapeutic and/or surgical treatment represent another situation where high-LET radiotherapy might offer some benefits over conventional radiotherapy. Such recurrences may derive from clones of cells exhibiting a resistance to conventional photon irradiation. Furthermore, the initial treatment may have compromised the vascularity, and the recurrent tumors may have a greater degree of hypoxia than tumors treated *de novo*. Two nonrandomized clinical trials support this hypothesis. Fermi Laboratories reported an 85% initial response rate, a 45% complete response rate, and an ultimate local control rate of 35% in 20 patients irradiated with neutrons for squamous cell carcinoma recurrent in regions that had received prior photon irradiation (Saroja et al, 1988). A report from Hammersmith on nine similar patients showed an 89% complete remission rate and 56% local control rate at 1 year (Errington and Catterall, 1986). The rate of significant treatment complications was about 25%.

Salivary gland malignancies

Based on the radiobiologic data of Battermann et al, salivary gland tumors exhibit very high RBEs for neutron irradiation (Battermann et al, 1981). They found an RBE of 8 for fractionated neutron radiation of acinic cell carcinoma metastatic to lung, which would indicate a very large therapeutic gain factor in using neutrons to treat this tumor system. Both phase II clinical trials and a randomized phase III study support this conclusion.

The randomized trial and the historical series are summarized in Table 4-1 (Laramore, 1987; Griffin et al, 1988). The data in this table is for patients treated for gross disease - either *de novo* or for tumor recurrent after surgery. Patients with microscopic residual disease after a surgical resection are not included. Although the number of patients in the randomized trial is quite small, the difference in the local control rates at 2 years is statistically significant ($p = 0.005$). The rates of complete tumor clearance in the cervical lymph nodes were 6 of 7 (86%) for the neutron group and 1 of 4 (25%) for the photon group. There was an association between improved local control and survival at 2 years - 62% for the neutron group versus 25% for the photon group ($p = 0.1$). Given the dramatic differences between the two groups of patients and historical control data that closely paralleled the trial results, it was thought to be unethical to continue the trial further. The participating neutron radiotherapy facilities now consider fast neutron irradiation the treatment of choice for patients with either inoperable lesions or with gross residual disease after surgery. Salivary gland tumors, of course, constitute a diverse spectrum of histologies and the fact that the number of patients in the randomized trial is small can certainly be criticized in this respect. However, analysis of the historical series seems to indicate that all histologies of salivary gland tumors respond equally well to fast neutron treatments. There was also no apparent difference between major and minor salivary gland tumors. Given the rarity of these tumors and the current opinions of the radiotherapy community, it is unlikely that the randomized trial will be repeated. However, data from larger patient series with longer follow-up times will continue to be of interest.

Table 4-1. Local control rates for salivary gland tumors treated definitively with radiotherapy

Photon radiation		
Historical data	61/254	24%
Randomized trial	2/12	17%
Neutron radiation		
Historical data	194/289	67%
Randomized trial	9/13	67%.

Charged particle radiotherapy

The use of "heavy" charged particles in radiotherapy allows the delivery of high radiation doses to tumors without causing much damage to the normal intervening tissue. In terms of the curves shown, this enables one to work at comparatively low doses on the normal tissue side effects curve and at high doses on the tumor response curve. The trailing edge of the Bragg peak for protons and alpha-particles falls off very rapidly because there are no fragmentation effects. With such beams it is possible to deliver very high doses to the target volume with millimeter precision. In certain cases such as juxtaspinal cord tumors, some head and neck sarcomas, and cordomas of the clivus, these beams are often the only way of delivering curative doses of radiation without causing life-threatening complications. Local control rates using this approach are excellent (Berson et al, 1988; Austin-Seymour et al, 1989). These beams are also used in the treatment of ocular melanomas wherein they

allow one to eradicate the tumor and preserve vision at the same time. A study is currently underway comparing this approach for ocular melanoma with ^{60}Co plaque therapy.

Hyperthermia and radiotherapy

Hyperthermia refers to the use of elevated temperatures in an attempt to control tumors. In killing cells with heat alone, the temperature to which the tissue is raised and the exposure time at that temperature are the critical factors. There are at least three basic mechanisms that have been proposed in heat-induced cell death: (1) altered membrane permeability, (2) microtubule breakdown, and (3) enhancement of antigen expression or antigen-antibody complexation.

A marked synergy has been demonstrated between hyperthermia and ionizing radiation. Tissue culture experiments show that the cytotoxic effects of these two modalities are additive in the G_1 phase of the cell cycle but are synergistic in late S phase. This may be due to inhibition of DNA repair by "heat shock" proteins or by alterations of cellular membrane structures important in the repair process. Hyperthermia also seems to inhibit repair of potentially lethal damage in G_0 phase cells. A low pH renders cells more sensitive to heat and in tumors, a low pH is generally associated with hypoxic cells. Hence, hyperthermia could potentially help to eradicate the fraction of cells most resistant to conventional photon irradiation.

The most significant impediment to a thorough study of hyperthermia is the inability to deliver and monitor thermal dosages in clinical trials. Methods of delivery include radiofrequency heating, use of microwaves, and ultrasound. In most cases the resulting temperature profiles are highly inhomogenous, making it difficult to address fundamental issues such as the optimal sequencing of the two modalities. The relatively superficial tumors of the head and neck may be easier to heat than more deeply seated tumors located elsewhere in the body, hence such tumors are of particular interest to workers in the field.

There are numerous reports of efficacy in terms of tumor response but few controlled studies. In a matched pair analysis, Scott et al demonstrated much faster response rates in superficially located tumors (Scott et al, 1984). Definitive phase III trials are lacking in this area.

Radiosensitizers and radioprotectors

Radiosensitizers are chemical agents that potentiate the effects of radiation. They should, ideally, be nontoxic in themselves. The basic idea is to increase the effect of the radiation on tumor cells but not on normal tissue and thus "separate" the two dose response curves. Hence, these agents must exploit some key differences between the two tissues. The halogenated pyrimidines such as BUdR (5-bromodeoxyuridine) are preferentially incorporated into the DNA of rapidly proliferating cells in place of thymidine. After their incorporation, the cells are able to repair radiation damage to a lesser degree. The application of these agents for head and neck cancer may be limited because the oral mucosa is a rapidly cycling tissue and is also sensitized. High electron-affinic hypoxic cell sensitizers such as misonidazole and SR-2508 preferentially sensitize hypoxic cells, which should be more common in tumors than in normal tissue. Many studies using misonidazole have been done: the results are quite

mixed. A review by Dische showed that misonidazole was beneficial in only 5 of 33 clinical trials involving various tumor sites (Dische, 1985).

More recently, several randomized trials using misonidazole have been carried out. As noted in the preceding section on altered fractionation, the EORTC conducted a trial combining misonidazole with an altered fractionation regimen and found no improvement in either local control or survival compared to a course of standard fractionation radiotherapy (van der Bogaert et al, 1986). A randomized trial was conducted in Denmark evaluating the effect of adding misonidazole to two different split-course radiotherapy regimens (Overgaard et al, 1989). A total of 626 patients was entered into the study. There was no difference in overall local control rates with the addition of misonidazole (37% versus 34%), but a subset analysis showed a benefit for the patients with pharyngeal lesions. The preirradiation hemoglobin level was also found to be of prognostic significance. The RTOG performed a trial of 298 patients, evaluating the addition of misonidazole to a "standard" course of radiotherapy (Fazekas et al, 1987, 1989). There were no significant differences in either local control or survival, and subset analysis failed to reproduce the results of the Danish group with respect to either pharyngeal primaries or pretreatment hemoglobin levels.

A problem with the use of misonidazole as a hypoxic cell radiosensitizer relates to peripheral neuropathy, which is its principal toxicity. This limits the amount of radiosensitizer that can be used, and it may well be that insufficient amounts have been used in the clinical trials reported to date. Work is in progress on new agents, SR-2508 and Ro-03-8799, that are more efficient radiosensitizers than misonidazole, and clinical trials using these agents may be more adequate tests of the radiosensitization concept.

Another approach to widening the therapeutic window is to shift the normal tissue response curve to the right without changing the position of the tumor response curve via the use of agents that selectively "protect" the normal tissues in the radiation field. The radioprotective agent studied most extensively thus far is a thiophosphate derivative of cysteine known as WR-2721. This compound probably protects cells by neutralizing intracellular free radicals before they can interact with the key target areas. Clinical work shows that it protects the bone marrow during hemibody irradiation (Constine et al, 1986). It is known that WR-2721 preferentially concentrates in the salivary glands, and thus it might be advantageous in reducing the xerostomia that is often a result of the radiotherapeutic treatment of head and neck cancer. New and more effective agents are being developed.